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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BRUMBACK, BRENDA G

ART UNIT	PAPER NUMBER
1642	7

DATE MAILED: 03/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,326	SATO ET AL.	
	Examiner	Art Unit	
	Brenda G. Brumback	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-8 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-8 are pending and examined on the merits.

Information Disclosure Statement

2. The information disclosure statement filed 12/22/2000 has been considered. A signed copy of the PTO-1449 is attached hereto.

Please note: The Sato et al. U.S. Patent Application Serial No. 09/269,332 listed in the IDS fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it is not a published document.

Claim Objections

3. Claims 1-8 are objected to because they lack proper introduction. The present Office practice is to insist that each claim be the object of a sentence starting with a phrase such as "I (or we) claim" or "What is claimed is" or "That which is claimed is". See MPEP 608.01 (m). Appropriate correction is required.

Claim 2 is objected to for the following informality: "receptor" is misspelled in line 2.

Specification

4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

The use of the trademarks QUICKPREP, POROS, SEPHAROSE, TWEEN, AMPLITAQ, GENECLEAN, QIAPREP, and GENETICIN has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 7, 26, 71-78, and 112 of copending Application No. 09/269,332. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to chimeric or humanized monoclonal antibodies for suppressing hypercalcemia associated with malignancy.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

6. Claims 2 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites an antagonist against a PTHrP receptor. While the specification discloses that an "antagonist" refers to a substance capable of inhibiting the binding of PTHrP and a receptor thereof, and includes antibodies, polypeptides, and "low molecular weight substances", the claim is indefinite because the metes and bounds of such a "low molecular weight substance" are not taught in the disclosure. Absent such teaching, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

Claim 4 is indefinite for recitation of a "fragment" of an anti-PTHrP antibody and a "modified form" of the fragment. The metes and bounds of such fragments and modified forms of the fragments are not taught in the specification. Absent this teaching, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

If applicant overcomes the present rejection under 35 U.S.C. 112, second paragraph, then a written description rejection that could have been made for the same claims will also have been overcome.

7. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is not clear from the disclosure that deposits of the 23-57-137-1 antibody meet all the criteria set forth in MPEP 608/01 (p)(C), items 1-3. Assurance of compliance may be in the form of a declaration or averment under oath. A suggested format for such a declaration or averment is outlined below:

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL

A declaration by applicant, assignee, or applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection and rejection based on a lack of availability of biological material.

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address.

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material will be irrevocably removed upon the granting of a patent.

5. States that the material has been deposited under conditions that ensure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 35 CFR 1.14 and 35 USC 122.

6. States that the deposited material will be stored with all care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case at least thirty (30) years after the date of a deposit or for the enforceable life of the patent, whichever is longer.

7. Acknowledges the duty to replace the deposit should the depository be unable to furnish a sample when requested due to the condition of the deposit.

8. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, name and address of the depository, and the complete taxonomic description.

As a possible means of completing the record, applicants may submit a copy of the deposit receipt.

8. Claims 1-5 and 7-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapeutic rodent monoclonal anti-PTHrP antibodies for administration to mice and for humanized anti-PTHrP monoclonal antibodies for administration to humans, does not reasonably provide enablement for therapeutic polypeptide antagonists of PTHrP or the PTHrP receptor, for low molecular weight" antagonists, for polyclonal or rodent monoclonal antibodies for administration to

humans, or for fragments and modified fragments of an anti-PTHrP antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a therapeutic agent for hypercalcemic crisis capable of inhibiting the binding between PTHrP and a PTHrP receptor, wherein the agent is an anti-PTHrP antibody, a humanized or chimeric monoclonal antibody, an antagonist against a PTHrP receptor, or a fragment or modified form of the fragment of an anti-PTHrP antibody.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that the efficacy of therapeutics is dependent upon factors such as solubility of the drug, bioavailability at the target site, attainment of effective plasma concentrations, solubility in tissues, biotransformation, toxicity, proteolytic degradation, immunological inactivation, rate of excretion or clearance (half-life), deactivation

by the liver, hydrolysis in serum, and binding to plasma protein. (see Benet et al., pp. 3-32, in The Pharmacological Basis of Therapeutics, 8th ed., 1990, page 3, first paragraph; page 5, second column, last partial paragraph, first two sentences; page 10, the paragraph bridging columns 1 and 2; page 18, the paragraph bridging columns 1 and 2; page 20, last full paragraph; and the paragraph bridging pages 20 and 21 and footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO BD> APP>& Inter. 1992). The art further teaches that peptide and polypeptide drugs have not met with success as therapeutics because they are destroyed in the gastrointestinal tract and because they do not readily penetrate cell membranes to reach the receptor biophase (see Farmer et al., TIPS, 362-365, September 1982, second paragraph of page 362). Rosen et al. (Calcif Tissue Int 61:455-459, IDS reference) teach that a peptide antagonist of PTH which has a high affinity for the PTHrP receptor *in vitro* is ineffective in humans for lowering serum calcium in patients with hyperparathyroidism (see the abstract). The art teaches that for efficacy and safety in humans, monoclonal antibodies must be humanized before they can be used as therapeutic agents (see Harris et al., TIBTECH, 11:42-44, 1993, especially page 42, second column, first full paragraph, and the paragraph bridging columns 2 and 3). The art does not teach therapeutic administration of antibody fragments and does not teach therapeutic administration of modified forms of antibody fragments.

The amount of direction or guidance present and the presence or absence of working examples: Given the teachings in the art regarding the unpredictability of peptide or polypeptide antagonists as therapeutics, administration of rodent monoclonal antibodies to humans, and therapeutic administration of fragments and modified fragments of antibodies, detailed teachings are required to be present in the specification. These teachings are absent. The specification discloses a humanized anti PTHrP antibody for therapeutic administration to treat hypercalcemic crisis associated with malignancy. The specification fails to teach non-humanized rodent monoclonal antibodies which can be therapeutically administered to humans, fails to teach fragments of humanized monoclonal antibodies which can be therapeutically administered for treatment of hypercalcemic crisis, and fails to teach antagonists other than humanized monoclonal antibodies which can be therapeutically administered. All of the working examples are drawn exclusively to a humanized monoclonal antibody directed against PTHrP.

The breadth of the claims and the quantity of experimentation needed: Because the claims encompass peptide antagonists against PTHrP receptors and antibodies and antibody fragments other than humanized monoclonal antibodies, because the art teaches that such antagonists and antibodies are unpredictable as therapeutics, and because the specification fails to contain sufficient disclosure to overcome the teachings of unpredictability which are found in the art, it would require undue experimentation by one of skill in the art to be able to make and use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

a. Claims 1-8 are rejected under 35 U.S.C. 102(a) as being anticipated by Sato et al. (WO 9813388, IDS item).

The claimed invention is drawn to a therapeutic agent for hypercalcemic crises associated with malignancy, wherein the agent is humanized anti-PTHrP monoclonal antibody 23-57-137-1.

Sato et al. teach humanized anti-PTHrP monoclonal antibody 23-57-137-1 for therapeutic administration to treat hypercalcemia caused by cancer.

b. Claims 1-3 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by any of Kanegafuchi Chem Ind. Co. Ltd. (JP 4-228089, of record in the IDS), Sumiya et al. (Saishin Igaku, 46/2:315-324, 1991), or Sato et al (Journal of Bone and Mineral Research, 8/7:849-60, 1993).

The claimed invention is drawn to a therapeutic anti-PTHrP monoclonal antibody for treating hypercalcemic crises associated with malignancy.

Kanegafuchi teaches a therapeutic anti-PTHrP monoclonal antibody for treating hypercalcemia (see the abstract).

Sumiya et al. teach anti-PTHrP monoclonal antibodies for treating hypercalcemia associated with malignancy (see the Dialog English abstract, JICST-Eplus, 01257066).

Sato et al. teach anti-PTHrP monoclonal antibodies for treating hypercalcemia associated with malignancy (see the abstract).

c. Claims 1-5 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoneda et al. (U.S. Patent 5,626,845).

Yoneda et al. teach a humanized monoclonal antibody directed against PTHrP for therapeutic administration to treat metastasis and osteolysis associated with cancer (see the abstract). Although Yoneda et al. disclose the antibody for treating metastasis, cancer cell growth, and osteolysis, rather than for treating hypercalcemic crisis, the portion of the claims which recites "for hypercalcemic crisis" is an intended use of the claimed composition and as such does not render the composition patentable over the composition of the prior art.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sato et al. in view of Yoneda et al.

The claimed invention is drawn to a therapeutic humanized anti-PTHrP monoclonal antibody for treating hypercalcemic crises associated with malignancy.

As set forth above, Sato et al. teach anti-PTHrP rodent monoclonal antibodies for treating hypercalcemia associated with malignancy in mice. Sato et al. differ from the claimed invention by teaching a rodent, rather than a humanized antibody; however, Sato et al. teach that development of a human monoclonal antibody would facilitate passive immunization as an effective therapy for malignancy-associated hypercalcemia in humans (see the last sentence of the sentence).

Yoneda et al. teach a humanized monoclonal antibody directed against PTHrP for therapeutic administration to treat metastasis and osteolysis associated with cancer (see the abstract).

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have administered the humanized antibody taught by Yoneda et al. as a therapeutic for hypercalcemic crisis according to the teachings of Sato et al.

Conclusion

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Kukreja et al. (Endocrinology 127/1 :305-310, 1990) teach that neutralizing antiserum reduces serum calcium levels and bone resorption in hypercalcemic athymic mice bearing a human squamous cell lung cancer (see the abstract).

Sato (Journal of Tokyo Women's Medical College, 58/9:939-946, 1988) teaches administration of an anti-PTHrP antibody as an effective treatment for malignancy associated hypercalcemia.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution

history or "DRAFT" for consideration by the examiner without entry. The Official FAX telephone number is (703) 872-9306 and the After Final FAX telephone number is (703) 872-9307. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Brenda Brumback
Patent Examiner